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AI-supported clinical decision systems optimizing multimodal PTSD treatment selection for veterans with co-occurring traumatic brain injury and depression

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Abstract

Post-traumatic stress disorder (PTSD) in military veterans frequently co-occurs with traumatic brain injury (TBI) and major depression, creating a complex clinical profile that challenges traditional treatment-selection approaches. Multimodal care including psychotherapy, pharmacotherapy, neurocognitive rehabilitation, and emerging neuromodulation techniques can improve outcomes, but determining the optimal combination for individual patients remains difficult due to heterogeneous symptom trajectories, overlapping neurobiological signatures, and varied treatment responses. This complexity has led to growing interest in artificial intelligence (AI)–supported clinical decision systems capable of integrating diverse data streams to guide personalized care pathways. AI-enabled platforms can analyze multimodal inputs such as electronic health records, neuroimaging markers, psychometric scales, behavioral data, and longitudinal treatment outcomes to generate predictive models for individualized therapy selection. Machine learning algorithms, particularly ensemble and deep learning architectures, are capable of identifying latent patterns linking neurocognitive impairment, affective dysregulation, trauma exposure profiles, and prior treatment responses to future clinical improvement. For veterans with co-occurring TBI and depression, these systems may help distinguish between PTSD-driven symptoms and TBI-related cognitive deficits, improving the precision of treatment assignments and reducing trial-and-error prescribing. Clinical decision systems also support multimodal treatment optimization by recommending combinations such as cognitive processing therapy with SSRIs, TBI-focused cognitive rehabilitation, or adjunctive neuromodulation based on predicted synergistic effects and individual risk factors. When integrated into clinical workflows, AI-supported tools can enhance early intervention, reduce care variability, and support measurement-based monitoring. By aligning clinical expertise with data-driven insights, AI-supported decision systems offer a scalable pathway for improving PTSD treatment outcomes in veterans with complex comorbidities. Their use has the potential to reduce symptom chronicity, enhance functional recovery, and support more efficient allocation of healthcare resources.

Keywords: PTSD; Traumatic brain injury; Clinical decision support; Machine learning; Multimodal treatment; Veteran mental health

1. Introduction

1.1. Clinical burden of PTSD in veteran populations

Post-traumatic stress disorder (PTSD) represents one of the most persistent and disabling conditions affecting veteran populations, with prevalence rates significantly higher than those observed in civilian groups [1]. Combat exposure, repeated traumatic events, and prolonged operational stress increase vulnerability to chronic PTSD trajectories, often

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leading to long-term psychological, social, and occupational impairment [2]. Veterans frequently present with intrusive memories, hyperarousal, sleep disturbances, emotional numbing, and impaired interpersonal functioning, all of which contribute to reduced quality of life and heightened healthcare utilization [3]. In many cases, PTSD is further associated with elevated risks of substance use, suicidal ideation, and cardiovascular morbidity, intensifying the clinical management burden placed on healthcare systems serving military personnel [4].

Moreover, delayed treatment-seeking behavior is common among veterans, driven by stigma, perceived weakness, or institutional barriers to mental-health services [5]. As a result, symptoms often become entrenched, reducing responsiveness to standard therapies and necessitating more complex clinical interventions [6]. Many veterans also struggle with reintegration into civilian life, where stressors such as unemployment, unstable housing, and limited social support exacerbate PTSD symptomatology [7]. The cumulative burden underscores the need for precise, individualized treatment decisions that consider both clinical and contextual determinants of recovery [8].

1.2. Overlap of PTSD, TBI, and depression: diagnostic and therapeutic complexity

PTSD rarely exists in isolation within veteran populations; instead, it frequently co-occurs with traumatic brain injury (TBI) and major depressive disorder (MDD), forming a clinical triad that complicates diagnosis and treatment [2]. Symptoms such as concentration difficulties, irritability, sleep issues, and memory impairment overlap across these conditions, making differential assessment challenging even for experienced clinicians [1]. This diagnostic ambiguity often results in misclassification or delayed identification of underlying neuropsychiatric drivers, thereby reducing the effectiveness of subsequent treatment pathways [4].

TBI adds another layer of complexity because its neurological effects may mimic or exacerbate PTSD symptoms, particularly in veterans with blast-related injuries [6]. Depression further amplifies functional impairment, contributing to emotional dysregulation, anhedonia, and motivational deficits that interfere with therapy engagement [3]. These intertwined symptom clusters often produce atypical response patterns to psychotherapy and pharmacological interventions, making standardized care models less effective for multimorbid veterans [8].

Therapeutic complexity is heightened by variability in severity, chronicity, and biological underpinnings across individuals [7]. For instance, patients with mild TBI may display cognitive vulnerabilities that hinder processing-based therapies, whereas those with severe depressive features may require integrated behavioral and pharmacological support [9]. This overlapping pathology reinforces the need for personalized approaches capable of disentangling symptom interactions and predicting optimal treatment responses [9].

1.3. Limitations of conventional treatment-selection frameworks

Traditional PTSD treatment-selection frameworks rely heavily on clinician judgment, broad diagnostic categories, and trial-and-error prescribing, making them poorly suited for veterans with complex comorbidities [3]. Evidence-based guidelines typically recommend trauma-focused psychotherapies and first-line medications, yet these recommendations assume homogeneity within diagnostic groups and do not account for neurocognitive differences, injury history, or symptom-interaction patterns common among veterans [1]. As a result, many patients experience incomplete remission, high dropout rates, and prolonged cycles of ineffective treatment attempts [4].

Conventional frameworks also overlook granular multimodal data such as neuroimaging findings, TBI severity markers, sleep metrics, and behavioral-engagement indicators that could meaningfully improve treatment matching [6]. In practice, clinicians may lack the time or resources to analyze complex datasets, resulting in underutilization of potentially predictive biomarkers [8]. Furthermore, standard protocols rarely incorporate longitudinal feedback loops that adapt treatment plans based on evolving symptom profiles, limiting responsiveness to clinical change [5].

The fragmentation between mental-health, neurological, and rehabilitation services further contributes to suboptimal care coordination, especially for veterans navigating multiple comorbidities [7]. Consequently, one-size-fits-all treatment strategies often fail to address heterogeneous needs, reinforcing the necessity of AI-driven models capable of integrating multimodal data to optimize individualized PTSD treatment pathways [9].

2. Pathophysiology and symptom interaction in PTSD–TBI–depression profiles

2.1. Neurobiological mechanisms linking trauma exposure, neural injury, and affective dysregulation

Trauma exposure initiates a cascade of neurobiological alterations involving the amygdala, hippocampus, and prefrontal cortex regions responsible for threat detection, memory consolidation, and emotional regulation [11]. In veterans, repeated combat stress amplifies these effects, producing hyper-reactive limbic circuits and weakened top-down inhibitory control, which contribute to persistent hyperarousal and maladaptive threat responses [14]. Traumatic brain injury (TBI) further disrupts neural pathways by damaging white-matter tracts and frontotemporal networks, impairing executive function, emotional processing, and attentional regulation [12]. These disruptions intensify PTSD symptomatology by impairing cognitive flexibility and increasing susceptibility to intrusive recollections [17].

Neuroendocrine dysregulation also plays a crucial role, as trauma alters hypothalamic–pituitary–adrenal (HPA) axis functioning, resulting in abnormal cortisol patterns that affect stress reactivity and mood stability [15]. Microstructural injury from blast exposure can additionally impair the default mode network, leading to disturbances in self-referential processing and emotional integration [18]. These combined neural changes explain why many veterans experience difficulty distinguishing between current environmental cues and trauma-linked memories, reinforcing cycles of anxiety and avoidance.

Neuroinflammatory responses triggered by both TBI and psychological trauma further contribute to mood dysregulation, cognitive slowing, and increased depressive features [19]. Ultimately, the convergence of neural injury and trauma-driven alterations produces a complex neurobiological phenotype that is difficult to treat using conventional, single-modal therapeutic strategies [13].

2.2. Cognitive, emotional, and behavioral symptom overlap: differential diagnosis challenges

PTSD, TBI, and depression share numerous overlapping symptoms, making differential diagnosis in veterans particularly challenging for clinicians [16]. Cognitive impairments such as memory deficits, slowed processing, poor concentration, and executive dysfunction appear in all three conditions, often masking underlying neurological injury or obscuring trauma-specific drivers of distress [11]. Emotional symptoms including irritability, anhedonia, guilt, and emotional numbing similarly overlap, complicating evaluation of whether mood disturbances stem from neurobiological injury, trauma-induced dysregulation, or depressive pathology [18].

Behavioral manifestations add another layer of complexity. Sleep disturbances, avoidance behaviors, impulsivity, and reduced motivation are core features of PTSD but also commonly follow concussive injuries or depressive episodes [15]. Such cross-cutting symptoms often lead to ambiguous clinical presentations, requiring detailed longitudinal assessment and multimodal diagnostic tools to distinguish between interrelated etiologies [12]. Misdiagnosis or partial diagnosis is common, especially when TBI-related symptoms mimic emotional dysregulation or when depressive features overshadow underlying trauma cues [19].

Moreover, psychological distress may interact with neurological deficits, creating hybrid symptom patterns not fully captured by standard diagnostic categories [14]. For example, a veteran with mild TBI may struggle with cognitive fatigue that reduces engagement in trauma-focused therapy, while depressive rumination may heighten sensitivity to PTSD triggers [17]. These interactions demonstrate that symptom clusters are rarely isolated; instead, they manifest synergistically, making single-diagnostic frameworks insufficient for accurate assessment [13]. Consequently, integrated diagnostic models capable of parsing symptom interdependencies are essential for effective clinical decision-making [16].

2.3. Implications of comorbidity for treatment planning and therapeutic sequencing

Comorbidity among PTSD, TBI, and depression significantly complicates treatment planning, as overlapping symptoms influence responsiveness to both psychotherapy and pharmacological interventions [11]. Veterans with cognitive impairment may struggle with the sustained attention required for exposure-based therapies, while those with depressive features often exhibit reduced motivation, impairing engagement and treatment persistence [15]. Similarly, neurological deficits may limit the effectiveness of cognitive restructuring techniques, requiring modifications in pacing, modality, or therapeutic intensity [18].

Pharmacological treatment becomes equally complex because medications targeting PTSD symptoms can worsen cognitive deficits associated with TBI or interact unfavorably with antidepressants prescribed for co-occurring mood disturbances [16]. Treatment sequencing is therefore critical: addressing severe depressive symptoms may be necessary before initiating trauma-processing interventions, while stabilizing neurological impairments may improve therapy readiness [12].

Comorbidity also increases the likelihood of atypical response profiles, necessitating adaptive, individualized treatment plans rather than linear, guideline-driven approaches [19]. These patterns highlight the limitations of traditional, siloed treatment frameworks and reinforce the need for integrated care strategies capable of capturing dynamic interactions among trauma, neural injury, and emotional dysregulation [17].

3. Multimodal data inputs for AI-driven treatment optimization

3.1. Electronic health records, psychometrics, and clinical trajectory data

Electronic health records (EHRs) provide foundational longitudinal data for understanding how PTSD, TBI, and depression evolve over time in veteran populations [20]. They capture diagnostic codes, medication histories, therapy participation, symptom fluctuations, and clinical encounters, enabling large-scale temporal analyses that can reveal patterns invisible in isolated assessments [23]. EHR-derived trajectory mapping is particularly valuable because veterans often cycle through multiple care settings, producing a diverse set of observations that AI systems can integrate into predictive analytics frameworks [24]. Psychometric assessments including PTSD severity scales, depression inventories, and cognitive-screening tools supply standardized quantitative markers that complement EHR narratives and enhance model precision [22].

Longitudinal symptom tracking is critical for multimorbidity, as PTSD symptoms may stabilize while cognitive impairments worsen or depressive features intensify, requiring dynamic analytic models that can adapt to shifting clinical states [28]. EHR data also contain comorbidity markers such as substance-use history, sleep disorders, and chronic pain, which commonly co-occur in veterans and influence treatment responsiveness [25]. Additionally, therapy engagement metrics including session attendance, completion rates, and dropout patterns provide behavioral signals that help machine-learning systems estimate adherence likelihood and treatment sustainment [26].

Combined, these EHR and psychometric datasets form a core multimodal foundation for AI-enabled clinical decision systems. They provide structured and semi-structured information needed to generate individualized predictions, helping clinicians navigate complexities inherent in PTSD–TBI–depression cases while reducing reliance on trial-and-error treatment selection [27].

3.2. Neuroimaging, biomarker profiles, and cognitive-function assessments

Neuroimaging constitutes one of the most informative modalities for characterizing the neurobiological disruption present in veterans with overlapping PTSD, TBI, and depression [21]. Structural MRI can identify cortical thinning, volumetric loss, and white-matter abnormalities associated with blast exposure or repeated concussive events [24]. Functional MRI and PET imaging further reveal altered connectivity patterns within emotion-regulation and attentional networks, providing quantitative markers that correlate with symptom clusters [20]. These imaging-derived signals enrich AI models by adding objective physiological measurements that differentiate trauma-driven dysregulation from injury-driven cognitive impairment [27].

Biomarker data including inflammatory cytokines, cortisol dysregulation profiles, and neurodegenerative markers offer another level of biological specificity [22]. Inflammatory signatures, for instance, can help explain persistent fatigue, cognitive slowing, and mood instability, while stress-hormone irregularities can indicate chronic hyperarousal linked to PTSD [28]. Molecular markers may also detect subtle neuronal injury even when imaging yields ambiguous results, strengthening diagnostic confidence [26].

Cognitive-function assessments encompassing executive function testing, memory evaluations, attention measures, and processing-speed tasks add essential behavioral correlates to neurobiological findings [25]. These measures help differentiate TBI-related cognitive deficits from trauma-induced disorganization or depressive slowing, providing critical context for AI-supported treatment stratification [23]. When integrated, neuroimaging, biomarker panels, and cognitive testing produce a multidimensional physiological profile that enhances model accuracy and supports individualized therapeutic targeting [21].

3.3. Behavioral, environmental, and digital phenotyping signals

Beyond clinical and biological data, behavioral and environmental signals play an increasingly important role in multimodal PTSD–TBI–depression modeling [28]. Wearable sensors and mobile devices can capture sleep patterns, physical activity, heart-rate variability, geolocation stability, and daily routine consistency indicators closely linked to symptom severity and relapse risk [24]. These digital phenotyping markers provide real-time, high-frequency observations that complement slower-moving clinical data streams, enabling AI systems to detect early warning patterns before clinical deterioration becomes apparent [27].

Environmental variables such as social-support availability, occupational stressors, and exposure to high-stimulation settings also influence symptom trajectories but are often missing from traditional assessments [20]. Integrating these contextual factors helps AI systems model how external pressures interact with underlying neurobiological vulnerabilities [23]. Behavioral data including communication patterns, engagement with digital platforms, and passive monitoring metrics can further reveal subtle functional impairments not captured during clinical visits [25].

Together, these behavioral and environmental streams complete the multimodal data ecosystem required for precision treatment selection.

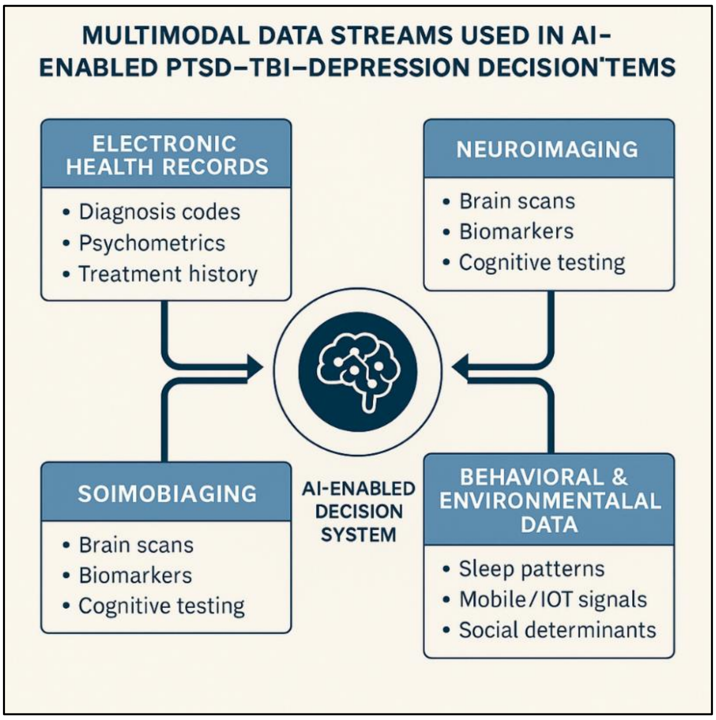

Figure 1 Multimodal Data Streams Used in AI-Enabled PTSD–TBI–Depression Decision Systems

4. AI architectures for personalized PTSD treatment pathways

4.1. Machine learning models for predicting treatment response

Machine learning (ML) has emerged as a powerful tool for predicting individualized treatment response in veterans with overlapping PTSD, TBI, and depression, largely due to its ability to uncover nonlinear patterns in complex, multimodal datasets [29]. Traditional statistical models often struggle to capture such heterogeneity, whereas ML approaches such as random forests, gradient-boosted trees, and support-vector machines can integrate symptom trajectories, psychometric scores, neurocognitive test results, and medication histories to infer which interventions are most likely to succeed for a specific patient [27]. These models identify subtle associations across datasets, detecting early predictors of psychotherapy dropout or pharmacological intolerance that clinicians may overlook when relying solely on experience or static guidelines [31].

ML treatment-response prediction models improve over time as additional patient data accumulate, enabling continuous recalibration of probability estimates and supporting adaptive personalization [33]. For example, ensemble methods can incorporate therapy engagement metrics, comorbidity patterns, and sleep-quality indicators to predict which veterans will benefit from cognitive processing therapy versus prolonged-exposure-based modalities [30]. Similarly, ML models trained on medication-response data can forecast the likelihood of adverse reactions or insufficient symptom reduction, facilitating earlier adjustments in care pathways [36].

These capabilities make ML essential for guiding individualized treatment selection in cases where multimorbidity generates atypical symptom presentations that defy traditional guideline-based approaches [34].

4.2. Deep learning for multimodal fusion of neurocognitive and affective datasets

Deep learning (DL) techniques excel in multimodal data fusion, making them particularly valuable for modeling the combined neurocognitive, emotional, and behavioral disturbances observed in PTSD–TBI–depression comorbidity [28]. Convolutional neural networks (CNNs) can extract high-resolution features from neuroimaging inputs such as fMRI connectivity maps or DTI-derived white-matter profiles capturing structural and functional disruptions linked to trauma exposure and neural injury [32]. Meanwhile, recurrent neural networks (RNNs) and long short-term memory (LSTM) architectures can model temporal changes in symptom severity, emotional variability, and sleep disruptions, providing dynamic representations of clinical evolution over time [37].

Multimodal DL frameworks integrate imaging, biomarkers, psychometrics, cognitive-performance data, and digital phenotyping signals into unified latent representations that capture relationships spanning biological, psychological, and behavioral domains [35]. This fusion enables the system to identify treatment-response signatures that emerge only when diverse data sources are jointly analyzed, such as patterns linking amygdala hyperconnectivity, inflammatory markers, and avoidance behavior to therapy non-response [27].

DL-based models also accommodate incomplete datasets by learning shared latent structures, allowing predictions even when certain modalities such as biomarkers or imaging are missing for a given individual [38]. This robustness is critical for real-world veteran care environments where data completeness varies widely. Ultimately, DL multimodal fusion supports deeper mechanistic understanding and more precise treatment stratification compared to traditional single-source analytical methods [31].

4.3. Reinforcement-learning and adaptive decision systems for dynamic treatment sequencing

Reinforcement learning (RL) provides a framework for modeling treatment planning as a sequential decision process in which the system learns optimal therapy strategies through iterative evaluation of patient outcomes [33]. RL-based models consider treatment selection not as a one-time choice but as an evolving sequence of decisions shaped by symptom changes, side-effect profiles, and engagement behaviors over time [29]. For veterans with multimorbid PTSD, TBI, and depression, this dynamic approach is especially important because symptom trajectories frequently shift in non-linear patterns influenced by neurological injury, environmental stressors, and fluctuating mood states [36].

RL systems use reward functions that encode therapeutic goals such as symptom reduction, cognitive improvement, or reduced relapse risk and update treatment strategies based on observed outcomes [28]. This allows the model to learn which interventions should be introduced, intensified, or discontinued at each stage of care. For example, RL may determine that initiating behavioral activation before trauma-focused psychotherapy produces better long-term outcomes in individuals with severe depressive features, whereas others may benefit from early cognitive rehabilitation due to TBI-related impairments [37].

Adaptive RL systems can also incorporate uncertainty and risk by factoring in the likelihood of dropout or adverse medication reactions, enabling more resilient treatment pathways [35].

Table 1 Comparison of AI Modeling Approaches for Multimodal PTSD Treatment Optimization

AI Approach	Primary Function	Strengths in PTSD–TBI–Depression Modeling	Limitations / Risks	Best Clinical Use Cases
Machine Learning (ML): Random Forests, Gradient Boosting, SVMs	Predicts treatment response and relapse risk using structured clinical and behavioral data.	• Interpretable models (relative to deep learning) • Handles nonlinear interactions well • Effective with limited or heterogeneous datasets • Good for early-stage triage and therapy-matching	• Limited ability to model high-dimensional imaging or biomarker data • Performance depends on feature engineering • Risk of bias if training datasets lack representativeness	• Predicting SSRI/SNRI response • Estimating risk of therapy dropout • Identifying candidates for trauma-focused psychotherapy
Deep Learning (DL): CNNs, RNNs,	Learns latent patterns across	• Excellent for high-dimensional and	• Requires large, balanced datasets	• Identifying neural signatures of

LSTMs, Multimodal Fusion Networks	neuroimaging, biomarkers, psychometrics, and digital phenotyping.	multimodal integration • Learns complex neurocognitive–affective patterns • Outperforms ML in imaging, EEG, and behavioral-stream modeling • Captures temporal dynamics of symptom evolution	• Low interpretability without XAI tools • Susceptible to overfitting with small or noisy datasets	therapy response • Detecting early neurocognitive decline • Integrating sleep, behavior, and imaging to refine treatment plans
Reinforcement Learning (RL)	Learns optimal, personalized treatment sequences over time based on outcome feedback.	• Models treatment as a dynamic, multi-stage process • Adjusts therapy recommendations as symptoms evolve • Incorporates side-effects, adherence patterns, and relapse signals • Supports long-term precision adaptation	• Requires longitudinal outcome data • Difficult to validate prospectively in clinical settings • Ethical concerns if recommendations appear opaque	• Sequencing psychotherapy + neuromodulation • Adjusting treatment intensity dynamically • Long-term follow-up planning and relapse prevention
Explainable AI (XAI)	Provides interpretability, transparency, and clinician-aligned reasoning for ML/DL/RL outputs.	• Enhances clinician trust and accountability • Identifies key drivers of treatment recommendations • Supports shared decision-making with veterans	• XAI tools vary in clarity and granularity • Partial explanations may oversimplify underlying m	

4.4. Explainable AI: transparency, interpretability, and clinician trust

Explainable AI (XAI) is essential for ensuring that clinicians trust and adopt ML, DL, and RL systems in PTSD–TBI–depression care pathways [30]. Many high-performing models especially deep architectures operate as "black boxes," making it difficult for clinicians to understand why a certain therapy or medication is recommended [34]. XAI tools such as SHAP values, feature-importance maps, and saliency visualizations help translate complex model outputs into human-interpretable insights that align with clinical reasoning [27].

Interpretability is especially critical in military and veteran-care settings, where transparency influences regulatory acceptance and ethical compliance [38]. By showing which factors such as cognitive scores, imaging findings, or behavioral patterns drove a recommendation, XAI strengthens clinician confidence and supports shared decision-making with patients [33]. This transparency bridges the gap between AI capabilities and practical clinical workflows, enabling precision treatment selection grounded in both data and clinician judgment [36].

5. Evidence-based multimodal treatment options for complex PTSD cases

5.1. Psychotherapies: CPT, PE, EMDR, CBT-I, and trauma-integrated modalities

Psychotherapy remains the therapeutic cornerstone for PTSD, especially in veteran populations presenting with overlapping TBI and depressive symptoms. Cognitive Processing Therapy (CPT) provides structured cognitive restructuring to address maladaptive trauma-related beliefs and has demonstrated strong efficacy even when depressive symptoms are prominent [38]. Prolonged Exposure (PE) therapy reduces avoidance patterns through systematic engagement with trauma memories and cues, although cognitive impairments associated with TBI may require pacing adjustments or auxiliary cognitive-rehabilitation supports [41]. Eye Movement Desensitization and

Reprocessing (EMDR) integrates bilateral stimulation with trauma recall, offering benefits for veterans who struggle with the high cognitive demands of PE or CPT [37].

Cognitive Behavioral Therapy for Insomnia (CBT-I) is particularly relevant, as sleep disturbances represent a central symptom cluster across PTSD, TBI, and depression, and sleep normalization often enhances responsiveness to other modalities [44]. Trauma-integrated modalities, including acceptance-based therapies and resilience-building interventions, offer flexible therapeutic structures that accommodate cognitive fluctuations common in mild TBI cases [39].

Clinical complexity arises when multimorbidity alters the sequence or intensity of psychotherapy. For example, severe cognitive fatigue may require shortened sessions, while persistent depressive features may necessitate behavioral activation prior to trauma-focused work [43]. Across modalities, individualized adaptation remains essential to sustaining engagement and improving long-term outcomes in complex veteran populations [45].

5.2. Pharmacotherapies: SSRIs, SNRIs, prazosin, novel investigational agents

Pharmacotherapy plays a central adjunctive role in treating PTSD–TBI–depression overlap, particularly when severe affective dysregulation or neurobiological instability limits engagement in psychotherapy. Selective serotonin reuptake inhibitors (SSRIs) remain first-line agents due to their broad efficacy across anxiety, depressive, and intrusive-thought symptoms, though treatment response may be attenuated in veterans with significant TBI-related network disruption [40]. Serotonin–norepinephrine reuptake inhibitors (SNRIs) provide an alternative mechanism of action and may offer enhanced benefits for comorbid pain syndromes, which frequently co-occur in this population [38].

Prazosin remains widely used for trauma-related nightmares and hyperarousal, addressing autonomic dysregulation that often exacerbates sleep disturbances and daytime irritability [42]. Investigational agents such as ketamine, MDMA-assisted psychotherapy, and neurosteroids have shown promise for refractory cases, particularly where traditional medications fail to achieve remission [37]. However, TBI-related vulnerabilities require careful consideration of dissociative or cognitive-altering effects when evaluating these treatments [45].

5.3. Neuromodulation and neurorehabilitation for PTSD with TBI comorbidity

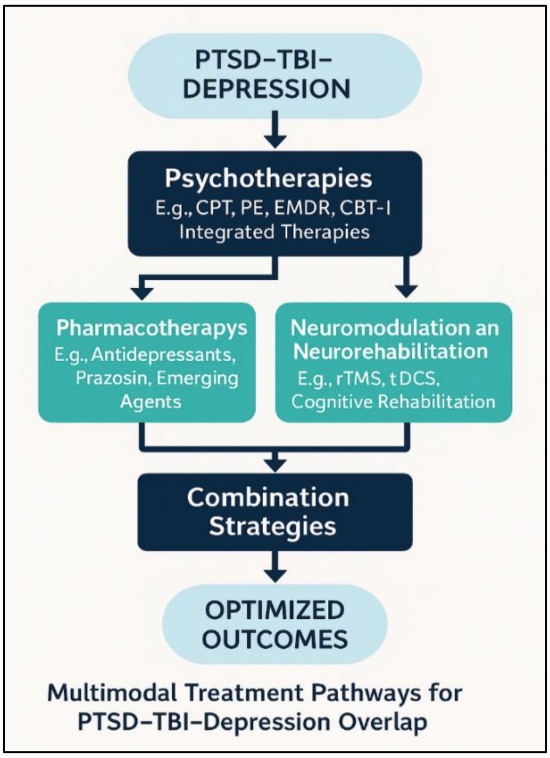

Figure 2 Multimodal Treatment Pathways for PTSD–TBI–Depression Overlap

Neuromodulation approaches have gained increasing interest for veterans whose PTSD symptoms coexist with significant TBI-related network dysfunction. Repetitive transcranial magnetic stimulation (rTMS) can modulate prefrontal–limbic circuitry implicated in emotional dysregulation and has shown meaningful reductions in hyperarousal and depressive symptoms in patients who have not responded to first-line therapies [41]. Transcranial direct-current stimulation (tDCS) and neurofeedback further target cortical connectivity abnormalities, offering adaptable, non-pharmacological strategies for addressing neurocognitive deficits [44].

Neurorehabilitation encompassing cognitive-remediation therapies, memory-training protocols, and compensatory-strategy coaching plays an essential role in enhancing executive function and improving capacity for psychotherapy engagement among individuals with TBI-linked impairments [39]. These modalities provide synergistic support when layered with trauma-focused interventions [43].

5.4. Combining modalities: sequencing, augmentation, and synergy models

Effective management of PTSD–TBI–depression overlap often requires combining modalities to match evolving symptom profiles [38]. Treatment sequencing is critical: stabilizing sleep with CBT-I or prazosin may improve readiness for trauma-focused therapy, while cognitive remediation may precede CPT for veterans with TBI-related impairments [45]. Augmentation strategies such as pairing SSRIs with neuromodulation or integrating EMDR with cognitive-enhancement protocols can achieve synergistic symptom reduction [40]. Multimodal pathways allow clinicians to adjust intensity, pacing, and therapeutic targets in response to dynamic clinical changes, improving long-term functional recovery in complex veteran populations [42].

6. AI-supported clinical decision systems in practice

6.1. Decision-support interfaces: risk scoring, therapy recommendations, and uncertainty ranges

AI-enabled clinical decision-support interfaces serve as the translation layer between complex predictive models and frontline clinicians treating veterans with PTSD–TBI–depression comorbidity. These interfaces typically combine risk-stratification dashboards with personalized treatment-recommendation modules, enabling rapid synthesis of multimodal data that clinicians would otherwise need extensive time to manually interpret [41]. Risk scoring incorporates neurocognitive profiles, symptom trajectories, biomarker patterns, and behavioral-adherence indicators, producing patient-specific severity and relapse-risk estimates that update dynamically with new information [40].

Treatment-recommendation modules provide prioritized therapy options such as CPT, EMDR, or rTMS based on predictive modeling of expected clinical response for a given individual [45]. These systems often include probability ranges, confidence levels, and uncertainty intervals, helping clinicians understand the strength of supporting evidence and model reliability [43]. Uncertainty quantification is particularly crucial when dealing with veterans who present with high symptom variability, incomplete diagnostic histories, or fluctuating cognitive capacity, as overly deterministic outputs could misguide decision-making [48].

Modern interfaces allow drill-down functionality, enabling clinicians to inspect the underlying factors that contributed to a recommendation, such as neuroimaging anomalies, sleep disruptions, or depressive-burden indices [50]. This transparency strengthens clinical trust and supports treatment planning that is both personalized and evidence-aligned [47]. Ultimately, intuitive decision-support tools help clinicians manage complex comorbidity patterns with improved precision and reduced cognitive workload [44].

6.2. Integrating AI outputs into psychiatry, neurology, and rehabilitation workflows

Integrating AI-generated insights into clinical workflows requires alignment with the operational realities of psychiatry, neurology, and physical or cognitive rehabilitation services. In psychiatric settings, AI-driven treatment suggestions must fit into standard diagnostic interviews, psychotherapy planning, and medication-monitoring routines without disrupting therapeutic rapport or workflow cadence [40]. For instance, risk-scoring outputs may be reviewed during case planning, while trajectory predictions may inform therapy sequencing for individuals with severe depressive or avoidance patterns [42].

In neurology, integration emphasizes harmonizing AI outputs with imaging interpretations, cognitive test results, and TBI-severity classifications. Clinicians may use model-based alerts to identify patients who could benefit from neuromodulation or neurorehabilitation interventions, particularly when traditional diagnostic markers are ambiguous [46]. Rehabilitation specialists benefit from AI tools that map cognitive-performance data, motor-function metrics, and behavioral signals to personalized rehabilitation plans, enabling more adaptive pacing and progress monitoring [49].

Multidisciplinary team meetings become a central hub for integrating recommendations across care domains, ensuring that predictive modeling informs shared decision-making rather than siloed interventions [43]. AI outputs may also be incorporated into telehealth platforms, enabling remote monitoring and early-warning alerts for veterans at heightened risk of symptom exacerbation or therapy dropout [45]. Effective integration requires minimizing redundancy, ensuring model explainability, and aligning digital workflows with clinician preferences to prevent alert fatigue and overreliance on automated judgments [48].

Table 2 Clinical Decision-Support Features and Their Operational Impact in PTSD Treatment Systems

Decision-Support Feature	Description / Functional Role	Operational Impact on PTSD–TBI–Depression Care
Risk-Stratification Scores	Aggregates multimodal data (symptoms, neurocognitive metrics, biomarkers, behavioral signals) into individualized severity and relapse-risk estimates.	• Enables early identification of high-risk veterans • Improves triage accuracy across psychiatry, neurology & rehabilitation • Supports proactive intervention planning
Treatment-Response Predictions	Uses ML/DL models to estimate likelihood of benefit from CPT, EMDR, SSRIs/SNRIs, neuromodulation, etc.	• Reduces trial-and-error treatment cycles • Matches veterans to the most appropriate modality earlier • Enhances long-term remission probability
Therapy Sequencing & Adaptive Pathways	RL-driven logic determines optimal ordering and timing of psychotherapy, pharmacotherapy, and neuromodulation.	• Supports dynamic care plans that adapt to symptom changes • Improves coordination across multiple specialties • Strengthens continuity of care
Uncertainty Quantification	Displays confidence intervals, probability distributions, and reliability ranges for all recommendations.	• Enhances clinician decision-making transparency • Prevents overreliance on flawed model outputs • Supports defensible clinical judgments
Explainable-AI Visualization Tools (XAI)	Highlights neural, cognitive, behavioral, or clinical features that influenced predicted outcomes.	• Builds clinician trust and accountability • Facilitates shared decision-making with veterans • Improves auditability for compliance reviews
Cross-Disciplinary Integration Panels	Combines psychiatry, neurology, rehab, sleep medicine, and behavioral-health insights into one unified dashboard.	• Reduces clinical silos • Supports multidisciplinary case-conference workflows • Enhances operational efficiency across VHA teams
Real-Time Monitoring & Alerts	Uses wearable and mobile data to detect symptom destabilization, medication non-adherence, or sleep disruption.	• Enables early warning for crisis prevention • Reduces ER visits and high-acuity incidents • Supports remote care for rural veterans
Workflow-Embedded Decision Prompts	Integrates recommendations directly into EHR, scheduling, telehealth, and medication-management platforms.	• Minimizes workflow disruption • Reduces clinician cognitive burden • Increases adoption of precision-care pathways

6.3. Safety, ethical guardrails, and clinician override policies

Implementation of AI-assisted PTSD–TBI–depression treatment systems requires stringent ethical, safety, and oversight mechanisms to ensure responsible use [41]. Safety protocols must address model drift, data-quality degradation, and misclassification risks that could result in inappropriate therapy recommendations for vulnerable veterans [47]. Ethical guardrails include fairness audits to detect bias within multimodal datasets, especially given known disparities in diagnosis and access among minority veteran groups [49].

Clinician override policies form a cornerstone of trustworthy deployment, ensuring that AI outputs augment rather than replace expert judgment [44]. Override mechanisms allow clinicians to reject recommendations when contraindications, contextual factors, or therapeutic intuition suggest alternative approaches. Such overrides must be tracked and analyzed to improve future model behavior, creating a feedback loop between clinicians and AI developers [50].

Privacy protections and strict data-governance controls are essential given the sensitivity of neurocognitive, behavioral, and psychiatric information used to power predictive systems [48]. These safeguards uphold veteran autonomy, institutional trust, and regulatory compliance while protecting against inappropriate secondary use of high-risk health data [46].

7. Implementation challenges, bias risks, and ethical considerations

7.1. Algorithmic bias, population-representativeness issues, and fairness in veteran subgroups

Algorithmic bias remains a central concern when deploying AI-enabled PTSD–TBI–depression treatment systems for veteran populations. Many machine-learning models are trained on datasets that do not adequately represent racial minorities, women veterans, rural veterans, or older service members, resulting in skewed predictions that may reinforce existing disparities in diagnosis, symptom interpretation, or treatment access [27]. Bias can arise from unequal sampling of neuroimaging data, limited psychometric representation across demographic groups, or behavioral datasets disproportionately derived from digitally engaged subpopulations [26].

In multimodal models combining EHRs, biomarkers, and digital phenotyping, missingness or lower-quality data for certain subgroups can contribute to distorted risk scoring and reduced treatment personalization [31]. For example, veterans with limited technology use may have fewer wearable-derived behavioral signals, leading models to underestimate sleep disruption or activity irregularities relevant to relapse risk [33]. Additionally, cultural differences in symptom expression such as communication patterns or avoidance behaviors may be interpreted inaccurately by AI systems lacking appropriate subgroup calibration [29].

Fairness requires continuous bias auditing, adaptive recalibration, and the development of subgroup-specific validation pipelines to ensure that AI recommendations achieve equitable predictive accuracy across the full veteran population [34].

7.2. Data governance, privacy protection, and secure interoperability

Robust data governance frameworks are essential for managing the highly sensitive clinical, neurocognitive, and behavioral information used in AI-assisted treatment systems [28]. PTSD–TBI–depression datasets often contain trauma histories, cognitive-function metrics, and neuroimaging results, all of which require strong safeguards to prevent unauthorized access or secondary misuse [31]. Privacy protections must ensure compliance with federal health-data regulations while supporting secure, multi-institution sharing needed for model training and validation [30].

Interoperability challenges arise when integrating disparate EHR systems, imaging platforms, digital-phenotyping devices, and rehabilitation databases, increasing risk of data leakage if transmission protocols are insufficiently protected [33]. Secure APIs, federated learning, and encryption-based exchange mechanisms help ensure continuous cross-system communication without compromising privacy or trust [26].

7.3. Clinical, legal, and institutional barriers to large-scale adoption

Despite the promise of AI-driven decision support, several adoption barriers persist within psychiatry, neurology, and rehabilitation systems that care for veterans [29]. Clinically, skepticism arises when models lack transparency or when clinicians have limited training in interpreting probabilistic outputs, leading to hesitation in incorporating AI recommendations into treatment plans [32]. Legal concerns include liability questions such as whether responsibility lies with clinicians, institutions, or developers when an AI-informed decision results in adverse outcomes [27].

Institutional barriers include insufficient digital infrastructure, limited funding for multimodal data integration, and variability in leadership buy-in across hospitals and veteran-care centers [34]. Furthermore, uneven availability of neuromodulation services, imaging resources, or digital-monitoring tools can limit the feasibility of AI-supported treatment pathways across facilities [31]. Addressing these constraints is essential for scaling AI deployment beyond isolated pilot programs [28].

8. Scaling ai-driven PTSD treatment systems across veteran health networks

8.1. Infrastructure requirements for VHA-wide implementation

Scaling AI-enabled PTSD–TBI–depression treatment systems across the Veterans Health Administration (VHA) requires substantial investment in data architecture, clinical platforms, and cross-site digital connectivity. Enterprise-wide integration demands interoperable EHR frameworks capable of aggregating multimodal data neuroimaging, psychometrics, biomarkers, and digital-behavioral signals at both regional and national levels [34]. Many VHA facilities operate on heterogeneous legacy systems, creating bottlenecks that limit standardized data flow and model deployment [39]. Robust computing infrastructure, including secure cloud environments and high-performance processing nodes, is essential for supporting continuous model updates, longitudinal risk scoring, and real-time decision support [36].

Given the sensitivity of veteran mental-health and neurocognitive data, infrastructure must include advanced encryption, role-based access controls, and audit trails to maintain privacy and operational integrity [41]. Additionally, telehealth integration is vital for ensuring that veterans in rural or remote areas receive algorithm-informed care, enabling equitable access across diverse VHA regions [37].

8.2. Training clinicians and support staff in AI-supported therapeutic planning

Successful adoption of AI-assisted treatment systems hinges on equipping clinicians, case managers, rehabilitation therapists, and administrative staff with appropriate training and decision-support literacy. Psychiatrists and neurologists must understand how risk scores, uncertainty ranges, and treatment-recommendation probabilities are generated, allowing them to contextualize outputs within real-world clinical judgment [35]. Without such knowledge, clinicians may either distrust AI insights or over-rely on them, undermining balanced integration into care pathways [42].

Training programs should emphasize explainability tools such as feature-attribution maps and model-derived treatment pathways that help clinicians interpret AI reasoning in a transparent and clinically aligned manner [38]. Simulation-based learning, case-based exercises, and multidisciplinary workshops can further enhance clinician comfort and highlight how predictive systems complement, rather than replace, existing protocols [40]. Establishing ongoing technical support teams ensures continuous feedback, rapid troubleshooting, and iterative improvement across VHA facilities [36].

8.3. Cross-agency collaboration and research-to-practice translation

Large-scale deployment requires collaboration between the VHA, the DoD, academic partners, and federally funded research programs to ensure harmonized standards and continuous validation of AI models [37]. Shared datasets, federated learning networks, and cross-agency working groups enable consistent calibration across diverse veteran subpopulations [41]. Research-to-practice pipelines must bridge evidence generation with operational integration, ensuring that algorithmic improvements translate rapidly into frontline mental-health, neurology, and rehabilitation settings [39]. Such collaboration strengthens national readiness and accelerates innovation across veteran-care ecosystems [34].

9. Strategic implications and future directions

9.1. Improving long-term outcomes through precision mental-health interventions

AI-enabled precision mental-health systems have the potential to dramatically improve long-term outcomes for veterans with overlapping PTSD, TBI, and depression. By integrating multimodal datasets ranging from neurocognitive assessments to behavioral patterns these models generate individualized treatment trajectories that adjust dynamically to changing clinical states [41]. Such personalization enhances therapy engagement and reduces relapse patterns that often emerge when standardized treatment plans fail to account for cognitive fluctuation or affective instability [44]. Predictive tools can also identify subgroups likely to benefit from neuromodulation, cognitive rehabilitation, or trauma-focused psychotherapy, enabling earlier intervention before chronic symptom cycles become entrenched [40].

In addition, risk-stratification analytics allow clinicians to anticipate escalation events, such as suicidal ideation or acute symptom destabilization, enhancing care coordination and crisis prevention [47]. As more data accumulate across VHA sites, precision models improve continuously, supporting long-horizon recovery trajectories and stronger reintegration outcomes for veterans navigating complex comorbidity profiles [49].

9.2. Enhancing system-wide efficiency through data-driven resource allocation

Large-scale deployment of predictive analytics within the VHA supports system-wide efficiency by enabling more strategic allocation of clinical, neuromodulation, and rehabilitation resources [43]. AI-driven workload forecasting helps identify which facilities will face increased demand for specialized therapies, such as rTMS or trauma-focused psychotherapy, allowing leadership to optimize staffing and reduce bottlenecks [40]. In rehabilitation and neurology settings, automated severity classification enables prioritization of high-acuity patients while streamlining routine follow-up consultations for stable individuals [48].

Resource planning also benefits from models that predict therapy dropout risk, enabling proactive outreach and targeted support for veterans most vulnerable to disengagement [46]. By strengthening operational foresight, AI systems reduce inefficiencies associated with uncoordinated scheduling, unnecessary referrals, or duplicative diagnostic procedures [50]. Ultimately, data-driven resource allocation supports more equitable access to care across geographically diverse VHA regions [42].

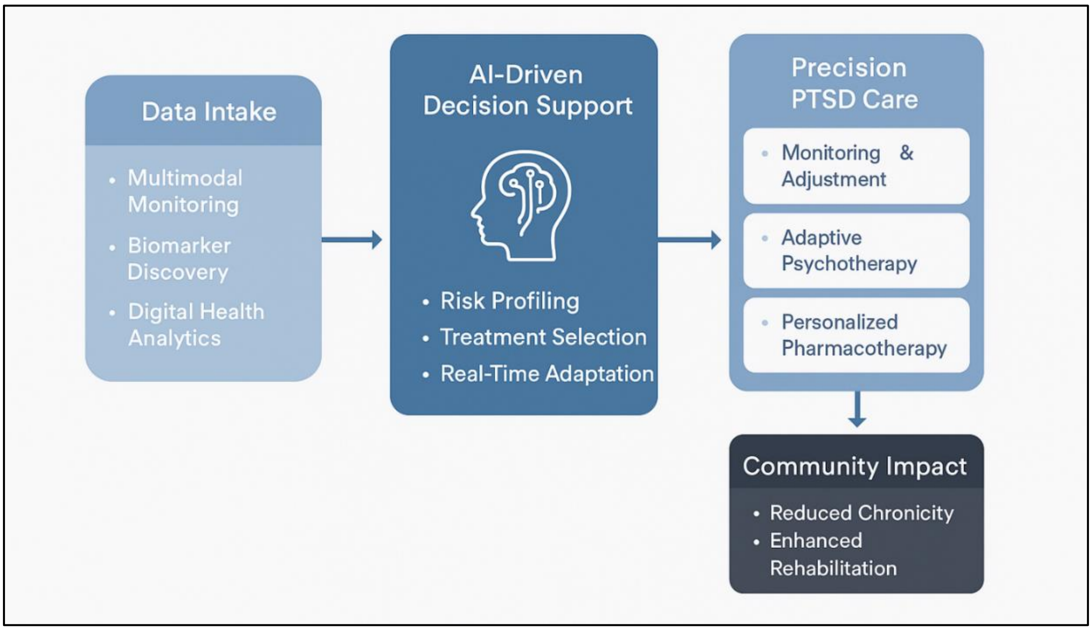

Figure 3 Future-State Framework for AI-Enhanced Precision PTSD Care in Veteran Populations

9.3. Future research priorities: biomarkers, real-time monitoring, and hybrid human-AI care

Future research must refine biomarker panels encompassing inflammatory signatures, neuroendocrine markers, and neural-connectivity indicators to improve mechanistic understanding and enhance prediction accuracy [45]. Real-time monitoring through wearables, mobile platforms, and passive behavioral sensing will allow earlier detection of symptom destabilization, expanding preventive care models [40]. Equally essential are hybrid care frameworks defining how AI systems collaborate with clinicians, balancing autonomy, ethical oversight, and personalized therapeutic judgment [49].

Advancing these priorities will ensure that precision mental-health care becomes both scientifically rigorous and operationally scalable across veteran populations [47].

10. Conclusion

The growing complexity of PTSD, TBI, and depression among veterans underscores the urgent need for clinical systems capable of integrating diverse data streams and translating them into precise, personalized treatment strategies. Traditional care pathways while effective for some cannot sufficiently accommodate the heterogeneous symptom patterns, cognitive fluctuations, and neurobiological disruptions that characterize this multimorbid population. As a result, treatment selection often becomes a prolonged process of trial and error, delaying recovery and placing significant strain on both patients and providers.

AI-enhanced multimodal decision systems offer a transformative solution. By unifying electronic health records, psychometric measures, neuroimaging data, biomarker profiles, cognitive-function assessments, behavioral indicators, and environmental signals, these models create a clinically meaningful representation of each veteran's unique symptom structure. Machine learning, deep-learning fusion architectures, reinforcement-learning treatment-sequencing tools, and explainable-AI interfaces together provide the analytical power needed to predict treatment responsiveness, anticipate risk trajectories, and dynamically adjust care over time. This multimodal capability is particularly essential for veterans who do not follow standard diagnostic patterns or who present with intertwined neurological and psychological drivers of impairment.

Unified decision-support systems extend beyond prediction: they enhance clinician insight, strengthen interdisciplinary collaboration, and reduce uncertainty in complex therapeutic planning. When embedded into psychiatry, neurology, and rehabilitation workflows, these systems act as adaptive companions enhancing rather than replacing clinical judgment and improving the timeliness and accuracy of treatment decisions.

At the system level, such technology can reshape veteran healthcare by streamlining resource allocation, enhancing crisis-prevention strategies, and supporting equitable access to advanced interventions across VHA facilities. In the long term, AI-driven precision care has the potential to significantly improve functional outcomes, reduce chronic disability, and enhance community reintegration for veterans navigating the combined burden of PTSD, TBI, and depression. Through sustained investment, ethical oversight, and cross-agency collaboration, these decision systems can become a cornerstone of modern veteran mental-health care delivering lasting value to individuals, families, and society.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

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